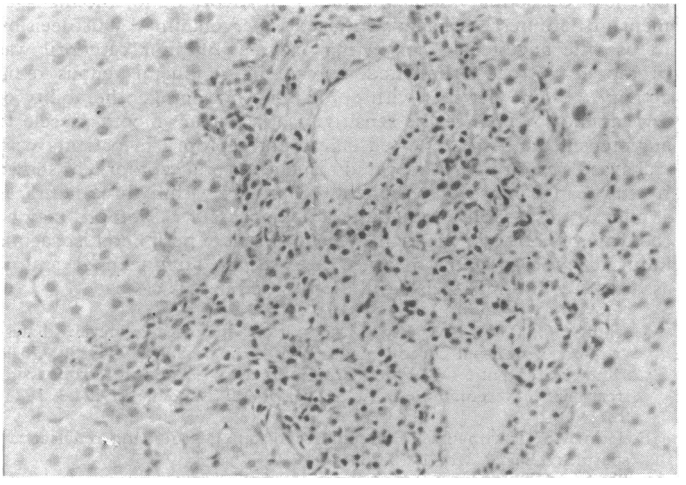
glutamic pyruvic transaminase activity 145 IU/l (normal range 1-40 IU/l); alkaline phosphatase activity 170 IU/l (normal range 29-48 IU/l); γ glutamyl transferase activity 568 IU/l (normal range 6-28 IU/l); and 17% eosinophils in peripheral blood. Markers for hepatitis A and B viruses, Epstein-Barr virus, and cytomegalovirus and autoantibodies were not found in the serum. A bile culture and tests for rheumatoid arthritis and lupus erythematosus yielded negative results. Ultrasonography of the liver confirmed hepatomegaly with no dilatation of the bile ducts. On 14 February blood tests showed serum glutamic pyruvic transaminase activity 108 IU/l; serum bilirubin concentration 21 μmol/l (1·2 mg/100 ml); alkaline phosphatase activity 175 IU/l; glutamyl transferase activity 419 IU/l; and eosinophils in the peripheral blood 9%. Laboratory findings on 26 February showed serum glutamic pyruvic transaminase activity 83 IU/l; serum bilirubin concentration 10 μmol/l (0·6 mg/100 ml); alkaline phosphatase activity 70 IU/l; γ glutamyl transferase activity 68 IU/l; and 2% eosinophils in peripheral blood. A percutaneous liver biopsy performed on the same day showed mixed inflammatory cells with infiltrates rich in eosinophils occupying the portal tracts; moderate cholestasis and slight increase in lipocytes were also noted. The lobular structure was normal (figure).

At the beginning of March he seemed well; all his symptoms had resolved and the liver was smaller. All laboratory findings were within normal limits.



Portal tract containing infiltrate of mixed inflammatory cells rich in eosinophils. Haematoxylin and eosin ×250.

Comment

In 1969 Ronnov-Jessen and Tjernlund first reported hepatic injury due to treatment with papaverine; their data suggested a hypersensitivity reaction.[2] A similar mechanism might therefore be expected with the papaverine derivative verapamil. Recently three cases of hepatotoxicity possibly induced by verapamil were described.[1 3 4] An allergic mechanism was supposed in all of them, but no histological study was performed. In our patient the absence of demonstrable viral infection, autoimmune disease, and intake of other toxic drugs supports the view that a syndrome similar to hepatitis can be caused by verapamil. An allergic pathogenesis is even more strongly indicated in this than in previous cases: the clinical picture, the interval (two weeks) between the start of treatment with verapamil and onset of symptoms, and the eosinophilia strongly suggest a hypersensitivity reaction. Furthermore, histological appearances in our patient were those typically described in idiosyncratic hepatic injury related to hypersensitivity[5] and were similar to those found by Ronnov-Jessen and Tjernlund in two of four cases of hepatotoxicity induced by papaverine.[2]

So far only a limited number of cases have been documented histologically, but the possibility that papaverine and its derivatives may cause hepatitis should be kept in mind if new cases with a similar histological picture are described. Physicians should be made aware that treatment with verapamil may occasionally provoke hepatic injury, and liver function tests should be monitored carefully in patients being treated with verapamil.

[1] Nash DT, Feer TD. Hepatic injury possibly induced by verapamil. *JAMA* 1983;**249**:395-6.

[2] Ronnov-Jessen V, Tjernlund A. Hepatotoxicity due to treatment with papaverine. *N Engl J Med* 1969;**281**:1333-5.

[3] Brodsky SJ, Cutler SS, Weiner DA, Klein MD. Hepatotoxicity due to treatment with verapamil. *Ann Intern Med* 1981;**94**:490-1.

[4] Stern EH, Pitchon R, King BD, Wiener I. Possible hepatitis from verapamil. *N Engl J Med* 1982;**306**:612.

[5] Zimmerman HJ, Ishak KG. Hepatic injury due to drugs and toxins. In: MacSween RNM, Anthony PP, Shever PJ, eds. *Pathology of the liver*. Edinburgh: Churchill Livingstone, 1979:335-86.

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L Spallanzani Hospital for Infectious Diseases, Rome, Italy

P GUARASCIO, MD, registrar
C D'AMATO, MD, senior registrar
P SETTE, MD, registrar
A CONTE, MD, registrar
G VISCO, MD, consultant physician

Correspondence to: Dr P Guarascio.

Cardiac arrest after reversal of effects of opiates with naloxone

Naloxone reverses respiratory depression after both anaesthesia and overdosage of narcotics and is also recommended in suspected opiate coma. Cardiovascular problems have developed after anaesthesia in patients given naloxone to reverse the effects of opiates.[1] We report on a patient addicted to narcotics who suffered ventricular fibrillation on four occasions after treatment with naloxone.

Case report

A 45 year old man presented with vomiting. He had drunk a bottle of spirits daily for over 10 years and had been admitted to hospital several times previously for conditions related to his alcoholic intake. We later learnt that he had also been taking up to 10 mg diamorphine daily for eight years. He showed signs of chronic liver disease, but pulse rate, respiration, blood pressure, a chest radiograph, and an electrocardiogram were normal. Liver function tests showed a pattern similar to that seen in hepatitis, and blood glucose concentration was 31 mmol/l (560 mg/100 ml). He was given an insulin infusion (3 U/hour), parenteral B vitamins, vitamin K, and chlormethiazole titrated to his withdrawal symptoms.

After 24 hours his condition was stable. Unknown to us, he then injected himself with diamorphine. Five hours later he became drowsy and then unrousable. A used syringe was near his hand, and an empty ampoule of diamorphine was found in his clothing. His wife, a fellow addict, later admitted to having smuggled these in. He was given two doses of naloxone 0·4 mg intravenously three minutes apart. Ventricular fibrillation was noted on the monitor three minutes later and responded to cardioversion. Blood glucose concentration was 11 mmol/l (198 mg/100 ml) and plasma potassium concentration 3·1 mmol(mEq)/l. He recovered consciousness but then relapsed into coma. He was intubated, and five minutes after two further doses of naloxone 0·4 mg intravenously he had another episode of ventricular fibrillation. He was defibrillated and given antiarrhythmic drugs. He recovered fully and discharged himself 10 days later.

Eight months later he was readmitted with symptoms of alcohol withdrawal. Signs, liver function, radiographic and electrocardiographic appearances, and treatment were as previously. He again surreptitiously injected himself with diamorphine and became comatose. Two doses of naloxone 0·4 mg intravenously were followed by one intramuscularly. His degree of consciousness improved, but after 30 minutes ventricular fibrillation supervened, necessitating defibrillation and infusion of lignocaine. Naloxone 0·4 mg was again administered intramuscularly, but ventricular fibrillation recurred 50 minutes later. Cardioversion and antiarrhythmic drugs maintained a stable cardiac output, but he died from hepatic and renal failure one week later. Postmortem examination showed hepatic cirrhosis and alcoholic cardiomyopathy.

Comment

Ventricular fibrillation has been reported after reversal of narcotic poisoning with nalorphine in a young woman presenting in casualty.[2] More recently seven cases of adverse cardiac effects after administration of naloxone during or after anaesthesia with opiates and nitrous oxide have been reviewed[1]; five patients had pre-existing cardiac disease, and the two others were fit young women. They showed either a rapid and substantial rise in blood pressure associated with atrial tachycardia and followed by cardiac decompensation, or ventricular fibrillation. In normal subjects anaesthetised with morphine and nitrous oxide,[3] and in patients addicted to narcotics, pulse rate and blood pressure increase appreciably after reversal of the effects

of opiates. Presumably naloxone antagonises opiate suppression of the sympathetic system resulting in a sudden increase in its activity.

Our patient had clinically unsuspected but pathologically proved cardiomyopathy. Cardiac arrhythmias are well recognised in patients with alcoholic cardiomyopathy as well as in heavy drinkers with no clinical evidence of heart disease.[4] We fear that in an emergency adverse cardiovascular reactions are seldom recognised as being due to reversal of the effects of opiates unless they occur repeatedly. In reversing opiate coma naloxone should be used cautiously and with electrocardiographic monitoring in patients with pre-existing cardiac disease or those predisposed to cardiac arrhythmias. Clonidine might possibly be useful because it abolishes increases in pulse and blood pressure after reversal of opiate effects with naloxone.[5]

[1] Pallasch TJ, Gill CJ. Naloxone associated morbidity and mortality. *Oral Surg* 1981;**52**:602-3.
[2] Lawrence JR, Lee FR. Ventricular fibrillation after narcotic withdrawal. *Lancet* 1975;ii:717.
[3] Desmonts JM, Bohm G, Conderc E. Hemodynamic responses to low doses of naloxone after narcotic-nitrous oxide anesthesia. *Anesthesiology* 1978;**49**:12-6.
[4] Ettinger PO, Wu CF, De la Cruz C, *et al.* Arrhythmias and the "holiday heart": alcohol-associated cardiac rhythm disorders. *Am Heart J* 1978;**95**:555-62.
[5] Fantozzi R, Luciani G, Masini E, *et al.* Clonidine and naloxone induced opiate withdrawal: a comparison between clonidine and morphine in man. *Subst Alcohol Actions Misuse* 1980;**1**:369-73.

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St Charles's Hospital, London W10
FRANCIS M CUSS, MA, MRCP, medical registrar
C BERNARD COLAÇO, MB, MRCP, medical registrar
J H BARON, DM, FRCP, consultant physician

Correspondence to: Dr F M Cuss, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London W6.

Treatment with captopril for peripheral ischaemia induced by ergotamine

Although clinical manifestations of ergotism have been known since antiquity, severe cases of ergotism are still occasionally encountered. Most of these are caused by overdosage of or undue sensitivity to ergotamine tartrate, which is used to treat migraine or as an abortifacient. Although peripheral ischaemia induced by ergotamine may resolve solely on withdrawal of the drug, this usually requires several days; in most cases active treatment is indicated to shorten the duration of ischaemia and reduce the risk of irreversible ischaemic damage. We report the rapid reversal of ischaemia induced by ergotamine on oral treatment with the angiotensin converting enzyme inhibitor captopril.

Case report

A 43 year old man was admitted to hospital with intense pains in his hands and feet, which had started one week earlier. He was a heavy smoker, consuming four packs of cigarettes daily. For 20 years he had been taking one to six tablets daily of a preparation containing ergotamine tartrate 2 mg. Within the past two years he had developed intermittent claudication and impotence. One week before admission he had developed a febrile disease with chills and a productive cough, which was treated with amoxycillin. His pains had started shortly thereafter.

On admission he was in intense pain. Temperature was 37·6°C and pulse rate 72 beats/minute and regular. Blood pressure could not be measured by sphygmomanometry. His hands and feet were cold, cyanotic, and pulseless. Carotid and femoral pulses, however, were present, and a Doppler examination produced flow murmurs over the popliteal, posterior tibial, brachial, and radial arteries. A chest radiogram showed infiltration of the right lower lobe. Routine biochemical investigation yielded unremarkable results except for a raised serum aspartate transaminase activity of 240 IU/ml and lactate dehydrogenase activity of 450 IU/ml; both reverted to normal within a few days.

Ergotamine tartrate was stopped, and captopril, 50 mg thrice daily by mouth, was given for four days. Within three hours after the start of treatment the brachial pulses became palpable, and within six hours all peripheral pulses could be palpated. This was accompanied by improvement in colour and temperature and the resolution of ischaemic pains. Within the following days perfusion remained excellent but burning, neuralgic pains developed on the soles of both feet. These were accompanied by reduced sensitivity to pain and vibration and impaired nerve conduction typical of peripheral ischaemic neuropathy. These abnormalities improved gradually throughout the following weeks.

Comment

Severe arterial spasm of the hands and feet is a well documented complication of treatment with ergotamine tartrate; its incidence is estimated at less than 0·01% in patients receiving therapeutic doses of the drug.[1] Factors that may aggravate ergotism or precipitate ergot toxicity include renal or hepatic insufficiency, thyrotoxicosis, and febrile diseases. In our patient, with chronic exposure to excessive amounts of ergotamine tartrate, pneumonia probably caused the sudden aggravation of symptoms.

Sympathetic blockade, surgical sympathectomy, low molecular weight dextran, anticoagulants, and intravenously or intra-arterially injected vasodilators such as tolazoline have been used to treat ergot toxicity with variable success. More recently sodium nitroprusside, a potent direct acting vasodilator, has been advocated for the management of peripheral ischaemia induced by ergotamine.[2] Our decision to use the angiotensin converting enzyme inhibitor captopril was prompted by the documented increase in peripheral venous renin activity in some patients with ergotamine poisoning,[3] the ability of ergotamine to enhance the sensitivity of vascular smooth muscle to angiotensin,[4] and the reported efficacy of captopril in patients with Takayasu's syndrome.[5] The rapid response to oral captopril, as shown by the reappearance of peripheral pulsations within three hours, is similar to the response to parenteral nitroprusside. Captopril may be the drug of choice in the management of severe peripheral ischaemia induced by ergotamine because it is easily administered and is associated with limited risk at the dose used in this case.

[1] Merhoff GC, Porter JM. Ergot intoxication: historical review and description of unusual clinical manifestations. *Ann Surg* 1974;**180**:773-9.
[2] Carliner NH, Denue DP, Finch CS, Goldberg LI. Sodium nitroprusside treatment of ergotamine-induced peripheral ischemia. *JAMA* 1974; **227**:308-9.
[3] Fedotin MS, Hartman C. Ergotamine poisoning producing renal artery spasm. *N Engl J Med* 1970;**283**:518-9.
[4] Gillman AG, Goodman LS, Gilman A, eds. *The pharmacological basis of therapeutics.* 6th ed. New York: Macmillan, 1980:939-47.
[5] Grossmann A, Knecht A, Rosenstein Z, Nussiniwitz N, Boykes C, Rosenthal T. Captopril therapy in Takayasu's syndrome [Abstract]. In: Hershko C. *Proceedings of the biannual congress of the Israel Society of Internal Medicine.* Tel-Aviv: Kenes, 1983:14.

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Shaare Zedek Medical Centre, PO Box 293, Jerusalem, Israel
ARI ZIMRAN, MD, resident in medicine
BOAZ OFEK, MD, resident in surgery
CHAIM HERSHKO, MD, professor of medicine

Correspondence to: Professor C Hershko.

Multiple spontaneous ruptures of tendons in renal transplant recipient

Spontaneous rupture of tendons has been described in patients with chronic renal failure[1-4] but not to our knowledge in recipients of successful renal transplants. We report multiple spontaneous ruptures of tendons that occurred five years after transplantation in a patient with good renal function.

Case report

A 40 year old man presented in 1971 with renal failure and heavy proteinuria (4·5 g/day). Chronic glomerulonephritis was diagnosed clinically because he had suffered from scarlet fever in childhood, showed no evidence of any systemic disease, and on intravenous urography had small kidneys without scarring or calyceal clubbing. Maintenance haemodialysis was started in